REMARKS/ARGUMENTS

Claims 1, 4-11, 21-23, and 26-33 are active. The claims have been revised for clarity and to conform to U.S. practice. Claim 1 and new independent Claim 30 further define the nature of the surface residues "J". Support for the polar group of J residues, i.e., Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Lys, Orn, Pro, Ser, Thr and Tyr is found on the top of page 11 of the specification. Particular J residues have been further defined in these claims based on the identity of the same J residues found in the sequences disclosed by SEQ ID NOS: 1-14. Briefly, the J residues in the sequence (PI) have been divided in 3 different groups:

Group 1 : the ones which always represent a polar amino acid selected from the group consisting in Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Lys, Orn, Pro, Ser, Thr and Tyr (these amino acids are J^{1}, J^{3}, J^{13}, J^{21}, J^{27}, J^{31}, J^{33}, J^{34}, J^{36}, J^{38}, J^{45}, J^{49}, J^{51}, J^{61}, J^{62}, J^{63}, J^{66}, J^{74} and J^{75});

Group 2 : the ones which do not represent such a polar amino acid (these amino acids are J^{14}, J^{26}, J^{64}, J^{69} and J^{71});

Group 3 : the ones which can represent such a polar amino acid but can also represent another amino acid (these amino acids are J^{2}, J^{4}, J^{5}, J^{6}, J^{9}, J^{10}, J^{23}, J^{24}, J^{28}, J^{30}, J^{35}, J^{39}, J^{41}, J^{42}, J^{43}, J^{46}, J^{47}, J^{48}, J^{53}, J^{54}, J^{67}, J^{70} and J^{73}).

The peptide sequence (PI) contains 47 amino acids "J" and the claims require at least 24 of these J residues to be selected from polar amino acids Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Lys, Orn, Pro, Ser, Thr and Tyr, thus meeting the limitation that at least 50% of the J residues are such polar residues.

New claims 30-31 find support in original claims 1 and 3 and on page 10 of the specification. In this claim, each amino acid J is defined by a Markush list of residues corresponding to residues disclosed by SEQ ID NOS: 1-14. Claim 32 finds support in original claim 9 and on page 13, line 23. Claim 33 finds support in original claims 7-8 and on page 13, lines 18-32. The particular residues required by claim 1 also find support in

Table 1 of the specification. As now claimed, the domain directly or indirectly interacting with the membrane lipids mainly comprises the residues 12, 15, 16, 17, 19, 20, 22, 50, 55, 57, 58, 59, 60 and 65 which consequently affect the peptide affinity for lipids and the stability and more generally the thermodynamic properties of the peptide subject-matter of the present invention mainly depend on the domain called "hydrophobic core" the residues of which are the residues U and B listed in Table 1. All these residues are clearly defined in sequence (I) and in Table 1. In view of the comments above, the Applicants do not believe that any new matter has been introduced.

Some Background on the Peptides of the Invention

Annexins are a family of peptides having common functions and about 70 amino acid residues (specification, page 3, lines 56-12). Members of this family have slight sequence homology but practically identical topology (specification, page 3, lines 14-17). As disclosed on page 15, line 20 *ff.* of the specification, the annexin-like peptide (PI) of the invention binds negatively-charged lipids (specification, page 3, lines 5 *ff.*). Amino acid residues, such as 12, 15, 16, etc. described on lines 20-21 of page 15 of the specification are involved in lipid binding. The amino acids "J" are the surface amino acids of the protein, while those identified as "U" are core residues (see page 16). As discussed in response to the first Office Action, the peptides of the present invention have improved properties in terms of affinity for phospholipids, toxicity, thermodynamic stability and reversibility of their folding processes when compared to prior art peptides.

The present invention concerns peptides directly or indirectly (e.g., via an intervening moiety) labeled with fluorine ^{18}F, derived from annexin domain 1 which have superior properties in terms of affinity for phospholipids, toxicity, thermodynamic stability and

reversibility of their folding processes when compared to prior art peptides such as those disclosed by Montaville et al., 2002, JBC, vol. 277, pages 24684-93.

Thanks to these superior properties and the direct or indirect labeling with a radioactive fluorine ^{18}F, a positron emitter, the peptides of the invention are useful for detecting not only *in vitro* but also *in vivo* apoptotic cells or foci, negatively charged lipids at the surface of the cells, etc.

Lack of Unity/Restriction/Election

The Applicants previously elected with traverse Group I. This requirement has been made FINAL. The non-elected claims have been cancelled without prejudice.

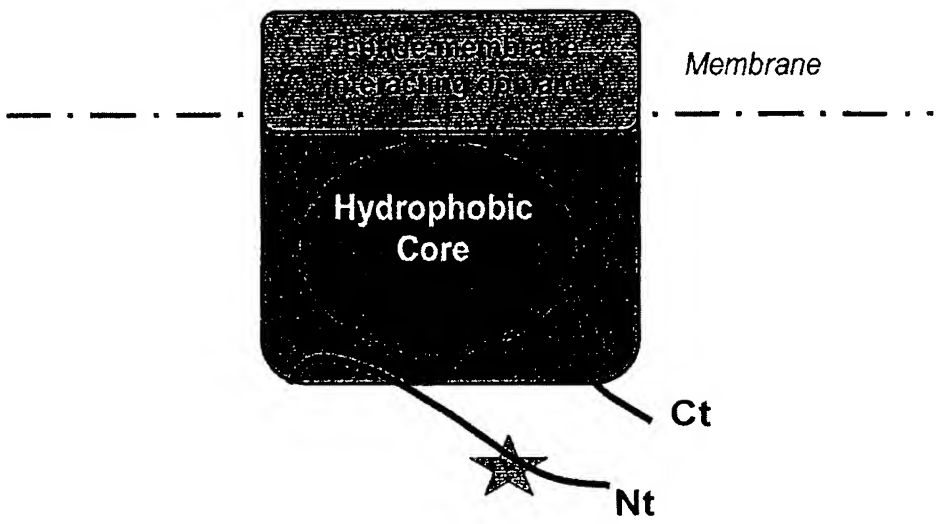
Rejection—35 U.S.C. §112, first paragraph

Claims 1-2, 5-11, 21-23, and 26-28 were rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description. This rejection is moot in view of the amendments above. Claim 1 is now directed to peptides labeled with the radioactive halogen fluorine ^{18}F (a positron emitter) which comprise the sequence (PI) where amino acids U and B appear as defined in Table 1 (which previously appeared in claim 3). The sequence listing describes the amino acids at positions 7, 14, 38, 62 and 75 within SEQ ID NOS: 1 to 14.

Claim 1 now specifically describes single amino acid selections at positions 7, 12, 14, 16, 17, 19, 20, 22, 32, 37, 38, 50, 55, 57, 58, 60, 62, and 75. "U" (core) residues at positions 8, 11, 15, 25, 29, 40, 44, 52, 56, 68 and 72 are described by a limited number of hydrophobic residues described in Table 1 included within the claim. Thus, 29 amino acids of the 75 amino acid residues in this sequence are specifically or narrowly defined by this claim. Moreover, the identities of the remaining amino acid residues (e.g., J or surface residues) are

limited to specific groups, for example, the amino acids at positions 59 and 65 must be chosen among the 4 following amino acids Glu, Asp, Lys and Arg.

Selection of these amino acids solves the technical problem depicted by the following diagram:



As explained in paragraphs [076] and [0082] of U.S. 2006/0233706, the domain that directly or indirectly interacts with the membrane lipids mainly comprises the residues 12, 15, 16, 17, 19, 20, 22, 50, 55, 57, 58, 59, 60 and 65. These residues, which are identified by claim 1, affect the peptide affinity for lipids.

The thermodynamic properties and stability of this peptide also depends on the hydrophobic core residues of which are the residues U and B shown in Table 1. The inventors discovered that by selecting particular combinations of hydrophobic residues improved the functional properties of the claimed peptides in comparison to annexin. The lower part of the peptide according to the invention includes, in particular, N-terminal and C-terminal segments to be used for various labelings (for example, positioned at the star of the diagram) and/or grafting on various supports.

For surface residues of the peptide according to the invention, other than those mentioned above, there is a certain freedom of choice. It should be noted however that some of these amino acids were set in the peptide sequence of the amended Claim 1 and on the basis of amino acids routinely found in the same position in SEQ ID NO: 1 to 14 of the sequence listing.

The peptide sequence of claim 1 comprises 75 amino acids of which 29 amino acids are identified by the base sequence of formula (I) or by reference to the choices required by Table 1. Nearly 50% of the amino acid sequence of the claimed peptide is identified by specific amino acid residues. Moreover, these amino acids are located at positions found to determine functional properties, such as binding affinity of the peptide for phospholipids, toxicity, thermodynamic stability and reversibility of their folding processes. Accordingly, in view of the amendments above which clearly describe the structure of the claimed peptides as well as providing a reasonable nexus between structure and function of particular core and surface residues, the Applicants respectfully request that this rejection now be withdrawn.

Rejection—35 U.S.C. §112, second paragraph

Claims 1-2, 5-11, 21-23 and 26-28 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. This rejection is moot in view of the amendments above.

Objection/Allowable Subject Matter

The Applicants thank Examiner Gupta for indicating that the subject matter of claims 4 and 27 is allowable.

Conclusion

This application presents allowable subject matter and the Examiner is respectfully requested to pass it to issue. The Examiner is kindly invited to contact the undersigned should a further discussion of the issues or claims be helpful.

Respectfully submitted,

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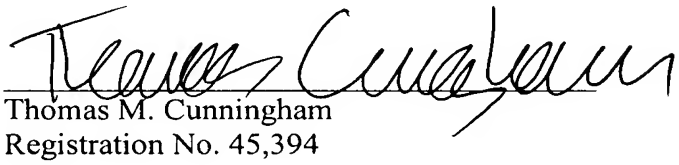
Norman F. Oblon



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